# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Premeeting briefing

## Mifamurtide for the treatment of osteosarcoma

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

IDM Pharma made an original manufacturer's submission to NICE in November 2008. An ERG report was sent to NICE in January 2009, and the Appraisal Committee discussed mifamurtide in February 2009. However, no appraisal consultation document was issued because the final price of the drug had not been formally announced by the manufacturer.

In June 2009 Takeda UK acquired IDM Pharma, including the rights to mifamurtide. In December 2009, Takeda UK provided an updated economic submission to NICE, which included a reassessment of the cost effectiveness of mifamurtide using a new economic model and a patient access scheme. The updated economic submission was reviewed by the ERG and NICE technical team and clarification questions were sent to the manufacturer. In February 2010, the manufacturer provided an addendum to the updated economic submission with an amendment to the proposed patient access scheme following a request from the NICE Patient Access Scheme Liaison Unit. The ERG provided an addendum to their original 2009 report, critiquing the updated manufacturer's economic submission (December 2009) and the addendum (February 2010).

**Original manufacturer's submission by IDM Pharma:**

**The manufacturer was asked to provide further details and analysis of the clinical study and give a further rationale on the assumptions used in the cost-effectiveness evaluation. The manufacturer was also asked to provide cost-effectiveness estimates for the six pairs of the four treatment groups, and complete further sensitivity analyses.**

**Updated economic submission by Takeda UK:**

**The manufacturer was asked to provide clarification on:**

- **details of the patient access scheme**
- **discrepancies in the economic model**
- **model inputs and assumptions**
- **incremental cost-effectiveness ratios (ICERs) derived from the probabilistic sensitivity analysis for all combinations of regimen.**

### Licensed indication

Mifamurtide (Mepact, Takeda UK) 'is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with postoperative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.'

## Key issues for consideration

- What is the Committee's view of the results of the pooled analysis comparing the effectiveness of mifamurtide-containing regimens A+ and B+ with chemotherapy regimens A and B?
- What is the Committee's view on the relevance of the post hoc subgroup analyses (requested by the ERG) that compared individual mifamurtide-containing regimens (regimen A+ or B+) with chemotherapy regimens (regimen A or B)?

- What is the Committee's view on the uncertainty in the manufacturer's base-case and post hoc subgroup analyses?
- What is the Committee's view on including the cost of adverse events, specifically hearing loss?
- What is the Committee's view on the uncertainty in the model associated with the following: whether all patients begin the model in the 100% disease-free state, whether age-related utilities are employed, and whether mortality rates reduce to those of the general population after 5 years without recurrence?
- Given that the manufacturer's cost-effectiveness estimates are all above £30,000 per quality-adjusted life year (QALY) gained, is there a case for supporting the technology as an effective use of NHS resources?

# 1 Decision problem

## *1.1 Decision problem approach in the manufacturer's submission*

Please refer to the original manufacturer's submission dated 13 November 2008.

| | |
|---|---|
| Population | Patients with high-grade resectable, non-metastatic osteosarcoma following surgical resection. |
| Intervention | Mifamurtide in combination with postoperative multi-agent chemotherapy, including doxorubicin, methotrexate, cisplatin and/or ifosfamide. |
| Comparators | Postoperative multi-agent chemotherapy alone |
| Outcomes | • Overall survival<br>• Disease-free survival<br>• Adverse effects of treatment<br>• Health-related quality of life (HRQoL) |
| Economic evaluation | Reference case: incremental cost/QALY, lifetime horizon<br>Perspective: NHS and personal social services perspective |

## *1.2 Evidence Review Group comments*

Please refer to the ERG report dated 6 January 2009.

### 1.2.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as patients with high-grade resectable, non-metastatic osteosarcoma following surgical resection. However, the original manufacturer's submission does not include any details of the mean age at diagnosis in the UK against which to compare the characteristics of patients in the clinical study.

### 1.2.2 Intervention

Mifamurtide is an immune adjuvant macrophage stimulant. The recommended dose for all patients is 2 mg/$m^2$ body surface area, administered by intravenous infusion (over 1 hour) twice-weekly for 12 weeks, with dosing at least 3 days apart. This is followed by once-weekly treatment for an additional 24 weeks (a total of 48 infusions over 36 weeks).

### 1.2.3 Comparators

The manufacturer's submission stated that the standard comparators to be considered are postoperative three- or four-agent adjuvant chemotherapy given alone; high-dose methotrexate, doxorubicin, and cisplatin with or without ifosfamide. The ERG stated that most chemotherapy regimens in UK clinical practice comprise doxorubicin, cisplatin and high-dose methotrexate. However, the most effective dosage of the combination of these agents has not been defined. The ERG stated that the use of ifosfamide as part of a four-arm chemotherapy regimen is uncommon in the UK. Ifosfamide is currently used in many centres across Europe. The ERG noted that it is not clear whether the four-agent combination offers a notable clinical advantage over the three-drug combination.

According to the clinical specialists advising the ERG, the options for second-line chemotherapy for recurrent osteosarcoma depend on the primary treatment. Second-line chemotherapy will often be based on high-dose methotrexate, ifosfamide and etoposide.

### 1.2.4 Outcomes

The following clinical outcomes were addressed in the manufacturer's submission: overall survival, disease-free survival, adverse effects of treatment and health related quality of life (HRQoL). The ERG considered these to be appropriate and clinically meaningful and there were no other valid outcomes that the ERG expected to be included.

### 1.2.5 Economic evaluation

Incremental cost per QALY gained was used as a measure of cost effectiveness, which is in accordance with the NICE reference case.

## *1.3 Statements from professional/patient groups and nominated experts*

Please note that the following statements are from November 2008.

Professional and patient groups stated that osteosarcoma is a rare primary malignant bone tumour, mainly affecting children and young people. Osteosarcoma is the most common bone sarcoma with approximately 120 new cases per year in England and Wales. Bone sarcomas are the second commonest cause of death from cancer in young people. The tumour typically arises in a long bone causing pain and swelling.

Professional groups stated that standard treatment comprises intensive combination chemotherapy given before and after surgical resection of the primary tumour. Chemotherapy regimens are reasonably well standardised. The current standard chemotherapy regimen consists of doxorubicin, cisplatin and methotrexate.

Professional and patient groups stated that there is little evidence of an improvement in the proportion of patients surviving over the past 20 years and that there have been no significant advances in systemic chemotherapy.

# 2 Clinical effectiveness evidence

## *2.1 Clinical effectiveness in the manufacturer's submission*

Please refer to the original manufacturer's submission dated 13 November 2008 and the ERG report dated 6 January 2009.

The manufacturer identified and presented data from one randomised controlled trial (RCT). The study (INT-0133) was a four-arm multicentre, open-label, active controlled, two by two factorial design study in patients with newly diagnosed high-grade resectable, non-metastatic osteosarcoma. Patients were under 30 years and were excluded if they had metastatic disease or unresectable primary disease, low-grade osteosarcoma, parosteal/periosteal sarcoma, radiation-induced sarcoma or osteosarcoma arising in premalignant bony lesions, or had received prior chemotherapy or radiation therapy.

The study included 678 patients from 178 centres which were primarily in the USA. Patients were recruited from November 1993 to November 1997. Follow-up data were collected until March 2007. Patients were randomised to the following:

- regimen A: methotrexate, doxorubicin and cisplatin
- regimen A+: regimen A plus mifamurtide
- regimen B: methotrexate, doxorubicin, cisplatin and ifosfamide
- regimen B+: regimen B plus mifamurtide

Patients received 10 weeks of neoadjuvant induction therapy with either chemotherapy regimen A or chemotherapy regimen B. Surgery was performed during weeks 10–11, while the patient was not receiving chemotherapy. Maintenance therapy was scheduled to begin at week 12 when patients received either regimen A or regimen B with or without the addition of mifamurtide. Patients randomised to receive mifamurtide in the maintenance phase received twice-weekly intravenous infusion of 2 mg/m$^2$ (which could be increased until biological activity was seen) for 12 weeks followed by once-weekly intravenous infusion for an additional 24 weeks, as a total of 48 infusions over 36 weeks.

**Results of the full analysis set**

The manufacturer presented analyses based on three data sets. The initial clinical study report presented data collected up to June 2003 (2003 data set), and August 2006 (2006 data set); an addendum subsequently provided the updated findings based on data to March 2007 (2007 data set). Both the manufacturer and the ERG considered the 2007 data set to be the most up to date and comprehensive of the study. This document reports the 2007 data set.

**Overall survival**

The overall survival data showed that the addition of mifamurtide to chemotherapy (regimens A+ and B+ combined) significantly improved overall survival compared with chemotherapy alone (regimens A and B combined: no mifamurtide). For the intention-to-treat population, the hazard ratio for death was 0.72 (95% confidence interval [CI] 0.53 to 0.97; p = 0.0313) at a median follow-up of 7.9 years.

**Disease-free survival**

The addition of mifamurtide to chemotherapy (regimens A+ and B+ combined) increased disease-free survival compared with chemotherapy alone (regimens A and B combined), although this was not statistically significant. For the

intention-to-treat population, the hazard ratio for remaining disease free was 0.78 (95% CI 0.61 to 1.01; p = 0.0586) at a median follow-up of 7.9 years.

**Results of the post hoc subgroup analyses**

The manufacturer undertook post hoc subgroup analyses on the overall survival data. These analyses showed a consistent increase in overall survival with mifamurtide plus chemotherapy compared with chemotherapy alone. This effect was independent of age, gender, ethnicity, study site, geographic location, tumour size, lactate dehydrogenase, alkaline phosphatase and background chemotherapy. Only one subgroup of patients (those over 16 years) did not benefit from the addition of mifamurtide to chemotherapy. The ERG requested an additional post hoc analysis that compared an individual mifamurtide-containing regimen (regimen A+) with a chemotherapy regimen most commonly used in the UK (regimen A). This analysis showed an improvement in overall survival (hazard ratio 0.75; 95% CI 0.49 to 1.16; p = 0.1949), corresponding to a non-significant 25% relative reduction in overall mortality.

The manufacturer also performed a post hoc subgroup analysis on the disease-free survival data at the request of the ERG. This analysis compared regimen A+ with regimen A and showed a non-significant improvement in disease-free survival (hazard ratio 0.96; 95% CI 0.67 to 1.38; p = 0.8357) corresponding to a 4% relative reduction in the risk of progression, recurrence or death.

The key results of the study are shown in table 1. The table provides a summary of the 2007 data set as reported by the manufacturer and constructed by the ERG.

**Table 1. Summary of main outcome of 2007 data set**

| Intervention[a] | Median follow-up (years) | Numbers followed in each group, n | Event in each group, n (%) | Hazard ratio (95% CI; p-value)[b] |
|---|---|---|---|---|
| ***Summary of overall survival using the 2007 data set*** | | | | |
| **A** | 7.8 | 174 | 51 (29%) | - |
| **A+** | 8.1 | 167 | 37 (22%) | - |
| **B** | 8.3 | 166 | 49 (30%) | - |
| **B+** | 7.4 | 171 | 36 (21%) | - |
| **Primary analysis** | | | | |
| A/B combined vs A+/B+ combined[c] | 7.9 | 340 vs 338 | 100 (29%) vs 73 (22%) | 0.72 (0.53 to 0.97; 0.0313) |
| **Post hoc analysis requested by the ERG** | | | | |
| A vs A+ | – | 174 vs 167 | 51 (29%) vs 37 (22%) | 0.75 (0.49 to 1.16; 0.1949) |
| B vs B+ | – | 166 vs 171 | 49 (30%) vs 36 (21%) | 0.68 (0.44 to 1.05; 0.0825) |
| ***Summary of disease-free survival using the 2007 data set*** | | | | |
| A (control) | 7.8 | 174 | 62 (36%) | - |
| A+ | 8.1 | 167 | 58 (35%) | - |
| B | 8.3 | 166 | 71 (43%) | - |
| B+ | 7.4 | 171 | 49 (29%) | - |
| **Primary analysis** | | | | |
| A/B combined vs A+/B+ combined[c] | 7.9 | 340 vs 338 | 133 (39%) vs 107 (32%) | 0.78 (0.61 to 1.01; 0.0586) |
| **Post hoc analysis requested by the ERG** | | | | |
| A vs A+ | – | 174 vs 167 | 62 (36%) vs 58 (35%) | 0.96 (0.67 to 1.38; 0.8357) |
| B vs B+- | – | 166 vs 171 | 71 (43%) vs 49 (29%) | 0.63 (0.44 to 0.91; 0.0144) |

[a] Regimen A: methotrexate, doxorubicin and cisplatin; Regimen A+: regimen A and mifamurtide; Regimen B: methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+: regimen B and mifamurtide.

[b] p-value from log rank test stratified by ifosfamide use and randomisation strata for regimens A+ and B+ combined vs regimens A and B combined; p-value from Cox model stratified by randomisation strata for pair-wise comparisons of regimens A, A+, B, B+.

[c] Test of the hypotheses of no interaction between chemotherapy intervention and mifamurtide did not meet the conventional level of significance of less than 0.1 (overall survival, p = 0.6; disease-free survival, p = 0.102). Therefore, marginal analyses were appropriate.

ERG, Evidence Review Group; CI, confidence interval.

## Safety

The original manufacturer's submission reports safety and tolerability data from the INT-0133 study. Additional safety data were reported from phase I and phase II studies.

A summary of the rates of discontinuation from the INT-0133 study, including reasons for premature termination (presented in table 2), suggests that mifamurtide in combination with multi-agent chemotherapy is reasonably tolerated. The rates of discontinuation were higher in both mifamurtide groups (regimens A+ and B+) than in the groups without mifamurtide (regimens A and B) during the adjuvant phase. Statistical analysis comparing the rates of discontinuation between the treatment groups was not reported in the original manufacturer's submission or in the requested supplementary data. The manufacturer stated that most of the withdrawals were because of toxicity that required significant intervention, were not life threatening and did not require mifamurtide therapy to be stopped. The manufacturer assumed that many patients, or their parents, withdrew from mifamurtide treatment because it was an investigational drug of unproven benefit and was uncomfortable or inconvenient (no further details were provided by the manufacturer) when added to an existing multi-agent chemotherapy regimen.

## Table 2 Number (%) of patients discontinuing treatment during the adjuvant phase of the INT-0133 trial

| | Interventions[a] (n) | | | | Primary analysis (n) | |
|---|---|---|---|---|---|---|
| | **Regimen A** | **Regimen A+ (includes mifamurtide)** | **Regimen B** | **Regimen B+ (includes mifamurtide)** | **Regimen A and regimen B combined** | **Regimen A+ and regimen B+ combined** |
| Subjects randomised | 174 | 167 | 166 | 171 | 340 | 338 |
| Subjects who received adjuvant therapy | 153 (88%) | 145 (87%) | 148 (89%) | 158 (92%) | 301 (89%) | 303 (89%) |
| Subjects who completed the study | 130 (75%) | 108 (65%) | 120 (72%) | 106 (62%) | 250 (74%) | 214 (63%) |
| Primary reason for premature termination during adjuvant phase | 23 (13%) | 37 (22%) | 28 (17%) | 52 (30%) | 51 (15%) | 89 (26%) |
| Progressive disease | 9 (39%) | 8[b] (22%) | 7 (25%) | 9 (17%) | 16 (31%) | 17 (19%) |
| Removed for toxicity | 1 (4%) | 1 (3%) | 4 (14%) | 2 (4%) | 5 (10%) | 3 (3%) |
| Withdrawal by parent or patient | 8 (35%) | 20 (54%) | 6 (21%) | 26 (50%) | 14 (27%) | 46 (52%) |
| Withdrawal by physician | 0 | 1 (3%) | 4 (14%) | 6 (12%) | 4 (8%) | 7 (8%) |
| Major protocol deviation | 2 (9%) | 5 (14%) | 5 (18%) | 4 (8%) | 7 (14%) | 9 (10%) |
| Death | 1 (4%) | 1 (3%) | 0 | 1 (2%) | 1 (2%) | 2 (2%) |
| Lost to follow-up | 0 | 1 (3%) | 0 | 1 (2%) | 0 | 2 (2%) |
| Other | 0 | 0 | 1 (4%) | 2 (4%) | 1 (2%) | 2 (2%) |
| Deemed ineligible | 2 (9%) | 0 | 1 (4%) | 1 (2%) | 3 (6%) | 1 (1%) |

Note: Percentages may not add up to 100% due to rounding.

a Regimen A: methotrexate, doxorubicin and cisplatin; Regimen A+: regimen A and mifamurtide; Regimen B: methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+: regimen B and mifamurtide.

b One patient had progressive disease documented at surgery. This patient is included among those with progressive disease.

In the INT-0133 study, only severe adverse events (grade 3 or 4) were reported. A summary of the pooled data (including data reported separately for each group) for serious and life-threatening treatment-related adverse events, as reported by the manufacturer and constructed by the ERG, is presented in table 8, page 37 of the ERG report. With the exception of hearing loss, the number of adverse events appeared to be similar across the combined treatment groups (no statistical analysis was reported in the supplementary data provided by the manufacturer). The manufacturer's submission suggests that mifamurtide significantly increased the incidence of objective hearing loss (11.5% with mifamurtide vs 7.1% without, p = 0.047) and subjective hearing loss (3.6% vs 0.6%, p = 0.007). The individual comparisons (presented in table 3) showed that the increased incidence of hearing problems occurred only in patients treated with three-arm chemotherapy plus mifamurtide (regimen A+) compared with those treated with three-arm chemotherapy alone (regimen A). The manufacturer's submission stated that hearing loss is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with mifamurtide was within the range expected for cisplatin alone.

**Table 3 Hearing loss related adverse events in the INT-0133 trial**

| | **Interventions a (n)** | | | | **Primary analysis (n)** | |
|---|---|---|---|---|---|---|
| | **Regimen A** | **Regimen A+ (includes mifamurtide)** | **Regimen B** | **Regimen B+ (includes mifamurtide)** | **Regimen A and regimen B combined** | **Regimen A+ and regimen B+ combined** |
| Number of patients | 174 | 167 | 166 | 171 | 340 | 338 |
| Hearing - objective | 8 (5%) | 26 (16%) | 16 (10%) | 13 (8%) | 24 (7%) | 39 (12%) |
| Hearing - subjective | 1(1%) | 10(6%) | 1(1%) | 2(1%) | 2 (1%) | 12 (4%) |

Regimen A: methotrexate, doxorubicin and cisplatin; Regimen A+: regimen A and mifamurtide; Regimen B: methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+: regimen B and mifamurtide.

Additional data (reported as a brief narrative summary on page 57 of the original manufacturer's submission) from phase I and II studies of over 700 patients suggest that mifamurtide is generally well tolerated. The original manufacturer's submission states that the most common adverse events in patients and healthy people treated with mifamurtide alone were fever, chills, fatigue, headache, nausea/vomiting, myalgia and tachycardia, hypotension, hypertension and dyspnoea. Chills, fever and pyrexia were reported as mild to moderate in severity and easily managed with paracetamol, without compromising treatment efficacy.

## *2.2 Evidence Review Group comments*

Please refer to the ERG report dated 16 January 2009.

The ERG identified several strengths in the manufacturer's clinical effectiveness evidence.

- The manufacturer's search strategy was well reported and the submission appears to contain all relevant head-to-head RCTs.
- The RCT measured a range of outcomes that were appropriate and clinically relevant.
- The statistical methods were well described.
- The submitted evidence adequately reflects the decision problem defined in the submission.

Areas of concern and uncertainty highlighted by the ERG on the clinical effectiveness evidence included the following.

- The manufacturer's process for data extraction and applying quality criteria to included studies was not explicitly clear in the manufacturer's submission. The ERG considered that this factor limited the robustness of the systematic review.

- Although the addition of mifamurtide to chemotherapy significantly improves overall survival compared with chemotherapy alone, the study was not adequately powered to assess this end point.

- The study protocol specified a 2 × 2 factorial analysis to assess two factors: chemotherapy (randomisation to one of two different chemotherapy regimens [regimens A and B] and mifamurtide [randomisation to receive mifamurtide or not]). The main analysis in the manufacturer's submission (using the 2007 data), was a factorial design (marginal analyses) and compared patients randomised to mifamurtide and multi-agent chemotherapy (regimen A+ and B+ combined) with patients randomised to no mifamurtide and multi-agent chemotherapy alone (regimen A and B combined). Although an independent analysis of the 2007 survival data by the Children's Oncology Group found that there was no evidence of interaction when mifamurtide was added to different chemotherapy treatments for both disease-free survival (p = 0.102) and overall survival (p = 0.60) (Meyers et al. 2008), the ERG considered the potential interaction as a key issue. The ERG requested that the manufacturer perform analyses comparing the individual mifamurtide-containing regimens with the three-drug chemotherapy control arm regimen (although the size of the study did not allow such comparisons to be made with reasonable statistical power). The ERG noted that when these analyses were undertaken by the manufacturer, the individual overall survival analyses showed that none of the comparisons were statistically significant. The ERG stated that it is unclear whether a more clinically relevant assessment for a UK population would be derived from an analysis comparing patients randomised to mifamurtide plus multi-agent chemotherapy (regimens A+ and B+ combined) with patients randomised to multi-agent chemotherapy alone (regimens A and B combined), or comparing an individual mifamurtide-containing regimen

(regimen A+) with a chemotherapy regimen most commonly used in UK clinical practice (regimen A).

- Although the ERG considered the INT-0133 study to be of reasonable quality, a number of design limitations were highlighted. The ERG stated that these limitations included:
    - the open-label design
    - delayed administration of mifamurtide (including failure to receive mifamurtide after randomisation)
    - an imbalance in histological response to neoadjuvant therapy between treatment groups (particular for those patients assigned to regimen A+, which had a greater proportion of patients with tumours showing a poor [5–100% viable tumour] histological response)
    - disparity of events (disease-free and overall survival) in the subset of patients who did not enter the maintenance phase, which may have influenced the results.
    - cisplatin was omitted in the ifosfamide-containing arms during the neoadjuvant chemotherapy phase. As a result, the role of ifosfamide is uncertain because its contribution as a substitute or adjunct is unclear.
- The INT-0133 study only included patients younger than 30 years of age with high-grade, resectable, non-metastatic osteosarcoma. The ERG noted that this comprises approximately 65% of all patients with osteosarcoma. The ERG stated that there is no information to support the use of mifamurtide in patients with osteosarcoma outside the eligibility criteria of this study.

- The rates of discontinuation from the INT-0133 study suggest that mifamurtide in combination with multi-agent chemotherapy is reasonably tolerated. Standard adjuvant chemotherapy in the UK (methotrexate, cisplatin and doxorubicin) is started 12 weeks after surgery and completed in approximately 30 weeks. A further 18 weeks of mifamurtide would be needed to be consistent with the schedule in the INT-0133 study. The ERG noted that a significant portion of patients with osteosarcoma are teenagers and young adults who may resist prolonged treatment. The commonest cause for declining randomisation in the European and American Osteosarcoma Study Group (EURAMOS) 1 study was considered to be a desire not to prolong therapy (Burnham et al. 2008).

## *2.3 Statements from professional/patient groups and nominated experts*

Please note that the following statements are from November 2008.

Professional groups stated that mifamurtide has only been used in the INT-0133 study and has not been available for patients since completion of the study in 1997. Professional groups commented that there is no information to support its use outside the eligibility criteria of the study, which was limited to those under 30 years without metastatic disease.

Professional groups highlighted two issues relating to the study. The first is whether ifosfamide was required to ensure activity of mifamurtide. They noted that in the initial report the benefit appeared to be confined to those randomised to receive mifamurtide in addition to ifosfamide. The professional groups reiterated that outside of clinical studies standard treatment is without ifosfamide. The second issue concerns the interpretation of the published reports of the study (Meyers et al. 2005, 2008). These relate to a possible interaction between the arms of the study. Professional groups stated that this uncertainty about the results would be resolved by a further clinical study.

Professional and patient groups noted that the evidence from clinical studies suggests that mifamurtide is a safe and well-tolerated treatment. Professional groups stated that if treatment is to be consistent with the schedule in the study, an additional 18 weeks of treatment will be required. Professional groups highlighted that a significant proportion of patients are teenagers and young adults who may resist prolonged treatment. However, a patient group stated that the potential benefits of the treatment mean that patients and families may be willing to prolong treatment.

# 3 Cost effectiveness

## *3.1 Cost effectiveness in the manufacturer's submission*

Please refer to the manufacturer's updated submission dated 10 December 2009 and its addendum dated 8 February 2010.

The manufacturer's updated economic submission incorporated a patient access scheme. Under this scheme there will be no charge to the NHS for the first 7 doses of mifamurtide.

The Markov model presented in the updated economic submission was based on the model in the original submission. The manufacturer reconstructed the original model in a different software package to the one used in the original submission in order to identify programming errors. For details of the programming errors identified, see table 3.1 on page 6 of the updated economic submission.

The new economic model had the same six health states as those used in original model, that is: disease free (start state), disease progression (start state), recurrence, recurrence disease progression, recurrence disease free, and death. The model had a cycle length of 6 months as in the original model, but with a time horizon of 60 years rather than 12.25 years. The manufacturer assumed that patients in the disease-free health state at 12.25 years had a mortality rate equivalent to the general population. Patients in the post-

recurrence disease-free state were assumed to have had a mortality rate dependent on the time to recurrence, which was derived from a study by Ferrari et al. 2003. For patients who had a recurrence within 2 years, the 6-monthly mortality rate was 14.87% and for those who had a recurrence after 2 years, the 6-monthly mortality rate was 4.98%.

The transition probabilities used in the deterministic base case in the new economic model were the same as those used in the original model. The transition probabilities were derived from the INT-0133 study for 604 patients who entered the maintenance phase, and the post-occurrence estimates were mostly derived from the literature, except when death was recorded as an event post recurrence.

The expected number of mifamurtide doses to be administered to each patient was assumed to be 48 in the original economic model. However in the updated economic model it was assumed to be 38.4. The manufacturer considered 38.4 doses to be more appropriate as there was a large variation in the number of doses that patients received (see table 4) and efficacy data in the original and updated economic model were based on the number of actual mifamurtide doses administered.

**Table 4 Mifamurtide dosing for patients receiving adjuvant therapy**

| Number of doses | Midpoint | Percentage of patients (%) |
|---|---|---|
| >50 | 53 | 1.7 |
| 46–50 | 48 | 51.7 |
| 41–45 | 43 | 10.2 |
| 36–40 | 38 | 7.4 |
| 31–35 | 33 | 4.0 |
| 26–30 | 28 | 5.1 |
| 21–30 | 23 | 6.3 |
| 16–20 | 18 | 2.8 |
| 11–15 | 13 | 2.9 |
| 6–10 | 8 | 3.4 |
| 1–5 | 3 | 4.5 |
| Average number of mifamurtide doses administered: 38.4 | | |

The utilities used in the original economic model were taken from a EuroQoL-5D (EQ-5D) survey of UK patients from the INT-0133 study and a review of NICE appraisals of cancer technologies. For further details see pages 75–9 of the original manufacturer's submission. However, in the manufacturer's updated economic submission, the figure of 0.75 derived from the EQ-5D survey was not considered to be realistic for the disease-free patient population because it was representative of older patients with end-of-life metastatic cancers. Therefore the figure of 0.85, derived from the NICE utility literature review, was considered more appropriate as patients in the model were disease free with an average age of 14 years. The specific utilities and source of utility for each health state are provided in Table 5, and age-related utility weights are provided in Table 6.

**Table 5 Health state utility values from the manufacturer's updated economic submission**

| Disease state | Base-case utility | Source |
|---|---|---|
| Disease progression | 0.39 | NICE HTA review. The HTA review provided an estimate of 0.44 for the disease progression to death category, which was adjusted by the –12% correction factor as above. |
| Disease free | 0.85 | It was determined that the figure of 0.75 derived from the EQ-5D survey was not realistic for this patient population and the figure of 0.85 derived from the NICE utility literature review was more realistic for patients who are of average age 14 years and currently disease free. 0.75 is a figure more representative of older patients with end-of-life metastatic cancers. |
| Recurrence | 0.61 | NICE HTA review. The HTA review provided an estimate of 0.69 for disease-progression/recurrence category. A correction factor of –12% was applied based on the ratio for the average utility for disease-free state in the EQ-5D survey and Alessi et al. 2007 (0.75) and the disease-free category in the NICE HTA review (0.85). |
| Disease free post recurrence | 0.85 | Assumed to be the same as disease-free value. |
| Disease progression post recurrence | 0.39 | Assumed to be the same as disease-progression value. |
| Death | 0.0 | – |

HTA: health technology assessment

**Table 6 Age-related utility weights from manufacturer's updated economic submission (UK population norms - EQ-5D)**

| Age (years) | Value |
|---|---|
| < 25 | 1.00 |
| 25–34 | 0.93 |
| 35–44 | 0.91 |
| 45–54 | 0.85 |
| 55–64 | 0.80 |
| 65–74 | 0.78 |
| 75+ | 0.74 |

The original manufacturer's submission and updated economic submission only included adverse events associated with infusion in the base-case analyses. From the INT-0133 study, hearing loss was identified as the main adverse event for mifamurtide. Disutilities associated with this adverse event were not included in the original or new economic models because it was considered to be an anomaly of the data; hearing loss is associated with cisplatin. A disutility factor of 18% for hearing loss was explored in sensitivity analyses in both the original manufacturer's submission and the updated economic submission. This was derived from one study found in a Medline search that contained a disutility factor of 18% for hearing loss in cancer patients.

The manufacturer's new economic model used the same categories of costs as those used in the original manufacturer's submission and included the following: adjuvant chemotherapy (cisplatin, doxorubicin, ifosfamide, methotrexate) with or without mifamurtide; treatment of adverse events during the maintenance phase; routine monitoring; diagnostics and surgery; and second-line chemotherapy for disease progression (ifosfamide and etoposide). However, in the manufacturer's new model costs and resource utilisation information was taken from the most recent NHS reference costs, that is 2007/08 rather than 2006/07 as used in the original manufacturer's submission. Information on healthcare resource use was not collected in the study. Therefore, the costs of these resources were estimated from information provided by clinical specialists. For further details of the unit costs used in the economic model, see manufacturer's updated economic submission page 18.

**Results**

The manufacturer's analyses incorporated a patient access scheme. Under this scheme there will be no charge to the NHS for the first 7 doses of mifamurtide. The main results of the manufacturer's new economic model are presented in table 7.

**Table 7 ICERs for all treatment regimens from the INT-0133 trial**

| | Regimen[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **A+/B+** | **A/B** | **Difference** | **A+** | **A-** | **Difference** | **B+** | **B-** | **Difference** |
| **Total costs** | £123,852 | £31,481 | £92,371 | £122,604 | £29,709 | £92,895 | £125,121 | £33,244 | £91,877 |
| **Mifamurtide drug costs** | £91,189 | - | £91,189 | £91,189 | - | £91,189 | £91,189 | - | £91,189 |
| **Adjuvant chemotherapy costs** | £26,205 | £26,205 | - | £26,205 | £26,205 | - | £27,625 | £27,625 | - |
| **Resource costs** | £6458 | £5277 | £1181 | £6631 | £4925 | £1706 | £6307 | £5619 | £687 |
| **QALYs** | 16.72 | 15.38 | 1.34 | 16.69 | 16.10 | 0.59 | 16.71 | 14.66 | 2.05 |
| **ICERs** | | | | | | | | | |
| **Incremental cost per QALY gained** | | £68,734 | | | £158,435 | | | £44,812 | |
| **ICER with PAS** | | £56,683 | | | £130,814 | | | £36,913 | |

[a] Regimen A: methotrexate, doxorubicin and cisplatin; Regimen A+: regimen A and mifamurtide; Regimen B: methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+: regimen B and mifamurtide; QALY: quality-adjusted life year; PAS: patient access scheme; ICER: incremental cost-effectiveness ratio.

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The manufacturer conducted a series of one-way sensitivity analyses based on the following model settings:

- Costs could vary by 40%, excluding drug costs, which are fixed.
- Mortality rates post recurrence and surgery and second-line chemotherapy at recurrence are assumed to vary within their 95% confidence interval.
- Recurrence rates and quality-of-life utility values varied between their 95% confidence interval, which was derived from assuming each utility value follows a beta statistical distribution and the total number of patients used to derive the utility values is based on the number of patients in the Alessi et al. 2007 study.
- Discounting varied between 0% and 6%.

The results of the sensitivity analysis showed that the model was sensitive to the discount rates used for outcomes and the health-related quality of life value for the disease-free health state (see pages 5–10 of the manufacturer's addendum to the updated economic submission).

The manufacturer's updated economic submission also presented a scenario analysis evaluating the effect of incorporating other model assumptions such as:

- incorporating amputation and limb salvage costs
- incorporating adverse events related to hearing loss
- allowing the post-recurrence mortality rate to equate to the general population mortality rate for patients who remain disease free after a given time period
- applying age-related utility rates.

The manufacturer defined their 'most pessimistic' scenario as their base case with all of the above assumptions included.

Results of the scenario analysis are presented in Table 8.

**Table 8 Key results provided by the manufacturer**

| Scenario | Deterministic ICER(£) | Probabilistic ICER(£) |
|---|---|---|
| MBC as detailed above | 56,683 | 54,830 |
| MBC but no PAS | 68,734 | Not reported |
| MBC with PAS but regimen A+ compared with regimen A | 130,814 | Not reported |
| MBC with PAS but regimen B+ compared with regimen B | 36,913 | 35,181 |
| MBC with PAS but discount rate for outcomes set to 0% per year | 22,262 | Not reported |
| MBC with PAS but discount rate for outcomes set to 6% per year | 92,806 | Not reported |
| MBC with PAS but amputation and limb salvage costs included | 59,231 | Not reported |
| MBC with PAS but hearing losses possibly associated with mifamurtide incorporated | 71,065 | Not reported |
| MBC with PAS but the mortality rate of the general population used for patients who had been disease free for 5 years | 61,580 | Not reported |
| MBC with PAS but age-related utility values applied | 62,112 | Not reported |
| Most pessimistic scenario | 91,442 | Not reported |

ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; MBC: manufacturer's base case.

The manufacturer also carried out probabilistic sensitivity analysis, with analyses assuming a willingness-to-pay threshold of £50,000. The results showed that approximately 30% of the iterations were below this limit.

## *3.2 Evidence Review Group comments*

Please refer to the addendum to the ERG report dated 12 February 2010.

The ERG considered that the new economic model structure was based on Markov model methodology which was appropriate and provided a fair assessment of the cost effectiveness of mifamurtide, although it did not estimate the same results as those observed in the trial. Both the population of the model and the 60-year time horizon were considered appropriate. The ERG noted that the updated economic model also incorporated the major health states for patients with osteosarcoma.

Areas of concern and uncertainty highlighted by the ERG about the cost-effectiveness evidence included the following:

- The base-case assumptions selected by the manufacturer were favourable to mifamurtide (consistently reducing the ICER), and as a result the base-case (deterministic) ICER of £56,683 per QALY gained for regimen A+/B+ compared to regimen A/B is likely to be substantially higher than that reported, particularly if regimen A+ versus regimen A is considered most appropriate to UK clinical practice.

**Treatment effectiveness**

- The lack of face validity of the new economic model. The ERG noted that the modelled survival rates at 6 years (83% and 77% with and without mifamurtide respectively) were greater than the observed data (80% and 73% with and without mifamurtide respectively) with increases in the range of 3 to 4 percentage points, and therefore a more appropriate time cycle should have been chosen. The ERG stated that although this lack of face validity increases the uncertainty

in the results, it is unclear what effect this would have on the ICER if the mortality rates observed in the INT-0133 study were replicated in the model.

- There was uncertainty associated with the ICER because of grouping of patients according to the number of doses of mifamurtide received, with the midpoint of the range used in the manufacturer's new model. The ERG noted that the manufacturer could have used the raw data to calculate the ICER but that the inaccuracy was unlikely to have a substantial effect.

- The rate of limb salvage used in the manufacturer's new model (75%) is based on UK rates which are slightly higher than the rates in the INT-0133 study (64%). However the ERG noted that this rate does not vary appreciably across treatment arms, therefore the impact on the cost-effectiveness estimate would be minimal.

**Health-related quality of life**

- The manufacturer's new model only included adverse events associated with infusion in the base-case analysis. The ERG noted that justification for the omission of hearing loss was based on clinical advice and that the most likely cause was treatment with cisplatin in combination therapy. Rates of hearing loss were consistent with current evidence. The ERG stated that it was unclear whether the loss of hearing observed when mifamurtide was added to chemotherapy regimens represented actual events or whether these were chance events associated with use of cisplatin. The ERG noted that while hearing loss is known to be associated with platinum-based treatment, it is not clear whether the observed data should be ignored, with the base case assuming no hearing loss. The ERG stated that incorporating a greater incidence of hearing loss associated with mifamurtide treatment increased the ICER.

**Resources and costs**

- Uncertainty around costs and resources was assumed to be a gamma distribution (with the assumption that the distribution had the same standard error as the mean). The ERG stated that this was incorrect for calculating the average cost, however this did not have a substantial impact and the associated increase in uncertainty because of inappropriate distributions was not thought to be large.

**Discounting**

- A discount rate of 3.5% was used in the manufacturer's base-case analysis, however other discount rates were explored. While the ICERs were insensitive to the discount rate for costs, a rate of 0% for utility decreased the base-case ICER to £22,254 per QALY gained, and using a rate of 6% for utility increased the base-case ICER to £92,806 per QALY gained.

## *3.3 Exploratory analysis by the ERG*

Please refer to the addendum to the ERG report dated 12 February 2010.

The ERG undertook a number of sensitivity analyses and all (apart from the discount rate which is specified in the NICE reference case) increased the cost per QALY gained compared with the manufacturer's base case. The results of the sensitivity analyses are presented in table 9. However, there is interaction between the parameters, and the ERG base case (scenario 14), which combines scenarios 1,4,5,6 and 7, has a cost per QALY gained below scenario 1 alone. This interaction was between scenarios 1 and 5, where only patients with regimen A and A+ were analysed, and the mortality rates set to that of age-matched general population if the patient was disease free for 5 years. In this instance the cost per QALY gained was reduced to £90,327; the reason for this interaction is unclear. The ERG noted that these sensitivity analyses did not adjust for the lack of face validity of the model, where the mortality rates modelled do not equate to those observed in the trial.

The ERG stated that the sensitivity analyses conducted indicated that with the patient access scheme, it is very unlikely that the cost per QALY gained is below £50,000 and that the most plausible value will be greater than £100,000.

**Table 9 Results from the ERG sensitivity analysis**

| Scenario code | Scenario description (see table 8 for more information) | Deterministic ICER (£) | Probabilistic ICER (£) | Proportion of PSA runs where ICER below £25,000 | Proportion of PSA runs where ICER below £50,000 | Proportion of PSA runs where ICER below £100,000 |
|---|---|---|---|---|---|---|
| MBC | Manufacturer's base case | 56,638 | 54,516 | 1% | 42% | 82% |
| 1 | MBC with PAS, but efficacy data used only from regimen A+ compared with regimen A. | 130,814 | 118,946 | 1% | 17% | 45% |
| 2 | MBC with PAS, but effects of observed hearing loss rates included | 71,065 | 67,994 | 0% | 27% | 71% |
| 3 | MBC with PAS, but 0.66% of patients start in the progressed disease state | 65,187 | 62,705 | 0% | 32% | 75% |
| 4 | MBC with PAS, but utilities dependent on age | 62,112 | 60,704 | 0% | 33% | 79% |
| 5 | MBC with PAS, but mortality rates set to that of age-matched general population if the patient was disease free for 5 years. | 61,580 | 60,637 | 0% | 33% | 80% |
| 6 | MBC with PAS, but limb salvage costs and amputation included. | 59,231 | 56,863 | 1% | 39% | 80% |
| 7 | MBC with PAS, but an assumption that 8% of patients would require 2 vials | 61,148 | 59,447 | 0% | 34% | 80% |
| 8 | MBC with PAS, but midpoints used to calculate number of vials used are decreased by one | 54,996 | 52,732 | 1% | 45% | 83% |
| 9 | MBC with PAS, but midpoints used to calculate number of vials used are increased by one | 58,370 | 57,762 | 1% | 38% | 79% |
| 10 | MBC with PAS, but PAS excluded | 68,734 | 66,730 | 0% | 25% | 75% |
| 11 | MBC with PAS, but cost inputs are assumed fixed | 56,683 | 54,830 | 1% | 42% | 81% |
| 12 | Discount rate for benefits set to 0% | 22,262 | 21,753 | 59% | 87% | 94% |

| Scenario code | Scenario description (see table 8 for more information) | Deterministic ICER (£) | Probabilistic ICER (£) | Proportion of PSA runs where ICER below £25,000 | Proportion of PSA runs where ICER below £50,000 | Proportion of PSA runs where ICER below £100,000 |
|---|---|---|---|---|---|---|
| 13 | Discount rate for benefits set to 6% | 92,806 | 90,038 | 0% | 5% | 57% |
| 14 | ERG base case | 109,296 | 103,494 | 0% | 13% | 48% |
| 15 | ERG base case but the observed rates of hearing loss incorporated | 164,202 | 147,494 | 0% | 7% | 36% |

MBC: manufacturer's base case; PSA: probabilistic sensitivity analysis; PAS: patient access scheme; ICER: incremental cost-effectiveness ratio

# 4 Authors

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# Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR):

- Pandor A, Fitzgerald P, Stevenson M, et al. Mifamurtide for osteosarcoma, January 2009.
- Stevenson M. Addendum critiquing the revised submitted economic model incorporating a patient access scheme, February 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Takeda UK (updated economic submission)
- IDM Pharma (original submission)

II Professional/specialist, patient/carer and other groups:

- Royal College of Nursing
- Royal College of Pathologists
- NCRI Sarcoma CSG, RCP, RCR, ACP, JCCO
- Bone Cancer Research Trust and Sarcoma UK
- Welsh Assembly Government

C Additional references used:

Burnham R and Whelan J (2008) Joint statement from NCRI Sarcoma CSG, RCP, RCR, ACP, JCCO to the National Institute for Health and Clinical Excellence.

Meyers PA, Schwartz CL, Krailo MD et al. (2005) Osteosarcoma: a randomised prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. Journal of Clinical Oncology 23: 2004–11.

Meyers PA, Schwartz CL, Krailo MD et al. (2008) Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival – a report from the Children's Oncology Group. Journal of Clinical Oncology 26: 633–68.